CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 09/28/95

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SUMMARY MINUTES

Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES
ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE #60

September 28, 1995
Holiday Inn Silver Spring
8777 Georgia Avenue, Silver Spring, MD

Members Present
Henry G. Bone, III, M.D., Chair
Nemat O. Borhani, M.D., M.P.H.
Joanna K. Zawadzki, M.D.
Colleen A. Colley, Pharm.D.
Cathy W. Critchlow, Ph.D.
Robert Sherwin, M.D.
Maria I. New, M.D.
D. Roger Illingworth, M.D., Ph.D.
Robert A. Kreisberg, M.D.

Members Absent
Jose Francisco Cara, M.D.
Robert Marcus, M.D.

FDA Participants
Solomon Sobel, M.D.
Gloria J. Troendle, M.D.
Leo Lutwak, M.D., Ph.D.
Bruce V. Stadel, M.D., M.P.H.
Joseph F. Contrera, Ph.D.
Lisa Stockbridge, Ph.D.

Guest Speakers
Lucien Abenhaim, M.D.
Stuart Rich, M.D.
Lewis Seiden, Ph.D.
Mark E. Molliver, M.D.

Executive Secretary
Kathleen R. Reedy, M.S.

These summary minutes for the September 28, 1995 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee were approved on _____.

I certify that I attended the September 28, 1995 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

Kathleen R. Reedy,
Executive Secretary

Henry G. Bone III, M.D.
Chairperson

Endocrinologic and Metabolic Drugs Advisory Committee Meeting #60

NDA 20-344, Dexfenfluramine Hydrochloride (Redux®)
Interneuron Pharmaceuticals Incorporated

OPEN SESSION

The meeting was called to order at 8:17 am by the Chair, Henry G. Bone III, M.D., who asked the Committee Members, Guest Experts and FDA staff at the discussion table to introduce themselves and mention the Institution with which they are affiliated. There were approximately 200 persons present at the meeting. The Committee members had been provided with background briefing books from both the Sponsor and the FDA.

Conflict of Interest

Full waivers were granted to Dr. Joanna Zawadzki and Dr. Cathy Critchlow. It was disclosed that invited Guest Speakers Dr. Stuart Rich and Dr. Lucien Abenhaim had been consultants to Servier and members of the Scientific Advisory Committee of International Primary Pulmonary Hypertension Study, which is the reason they were invited to speak.

OPEN PUBLIC HEARING

Barbara C. Hansen, Ph.D., *President, American Society for Clinical Nutrition* and Director, Obesity and Diabetes Research Center, Department of Physiology, University of Maryland School of Medicine, reminded the Committee of her research with diabetic and obese primates which she had presented to the Committee at a previous meeting. She spoke of the new genetic research but also of the need for a tool now, in addition to diet and behavior modification to address the disease of obesity.

Judith S. Stern, Sc.D., *Vice President, American Obesity Association*, and Professor of Nutrition and Internal Medicine, University of California-Davis echoed Dr. Hansen's comments. She spoke of the Institute of Medicine's report "Weighing the Options" that suggests the epidemic of obesity be addressed with new strategies. The study estimates that one third of the population is overweight, and the resulting co-morbid conditions increase their mortality

SPONSOR PRESENTATION

Interneuron Pharmaceuticals Incorporated
NDA 20-344, Dexfenfluramine Hydrochloride (Redux®)

Introduction: **Glenn L. Cooper, M.D.** introduced the topics to be addressed in the presentation and the speakers. He defined obesity as a serious disease, reviewed the history of the drug dexfenfluramine and gave an overview of the studies.

Obesity - Need for Treatment:

Theodore VanItallie, M.D., described the toll of preventable disease and death caused by obesity as second only to smoking. He presented National Center for Health Statistics criteria for obesity by body mass index and data showing that one third of the population is obese.

JoAnn Manson, M.D., Dr.P.H., discussed the results of the Nurse's Health Study; 115,000 U.S. women between the ages of 30 and 55, which showed that a BMI of 27-29 increases the risk of premature mortality by 60%.

George Bray, M.D., addressed the concern that obesity related illness and disease increase the cost of health care. He suggested the attributable risk reduction in diabetes, heart disease, dyslipidemia, hypertension, and other obesity related disease of a 20 pound weight loss could reduce health care cost by over 30%. He discussed intervention for prevention of weight regain.

Mechanism of Action: **Richard J. Wurtman, M.D.,** introduced the pharmacology of dexfenfluramine, pointing out that it is a serotonin rather than a dopamine drug. He described the mechanism of action, differentiating it from an amphetamine, and stated that it has no effect on norepinephrine. He demonstrated the pharmacokinetics, and declared the treatment effective, regardless of the cause of the obesity.

Neurochemical Effects of Large Doses: **Robert Y. Moore, MD, PhD,** discussed evidence that this drug has a pharmacologic action rather than a neurotoxic one. He described neurons, their axons, their location in the brain, the degeneration and regeneration of neurons, and some observations in animals.

Efficacy and Safety: **Bobby W. Sandage, Jr., Ph.D.,** described the four clinical trials with dexfenfluramine, showing efficacy analyzed in alternative ways discussed in FDA guidance. The largest and longest measured multiple dose regimens and tracked some co-morbid conditions.

Special Safety and Overall Risk/Benefit: **Gerald A. Faich, M.D., M.P.H.,** reviewed the risks and benefits of the drug, including primary pulmonary hypertension and multiple co-morbid risks at body mass indices above 27, discussing the analyses and odds ratios of each and combinations of risks.

Lack of Abuse Potential: **Theodore J. Cicero, Ph.D.,** pointed out that in 1973, fenfluramine and its isomers were scheduled as an abusable substance. Dexfenfluramine, an isomer of fenfluramine, has had no incidents of abuse reported since 1980. An enormous amount of pre-clinical and wide-scale epidemiological studies have been done, 30 million persons exposed, with little abuse.

Conclusion: **Louis Lasagna, M.D.,** drew a parallel of the health threat of hypertension 15 years ago, and the global response to solve and control the condition, with the present threat of obesity, suggesting the need for rapid and effective response.

GUEST EXPERT SPEAKERS

<u>International Primary Pulmonary Hypertension Study</u>

Overview of the IPPH Study by the Principal Investigator: **Lucien Abenhaim, M.D.,** Director, Center for Clinical Epidemiology and Community Studies, McGill University, Jewish General Hospital, Montreal, Quebec, Canada, stated that the group was convened following a cluster of fenfluramine associated cases in France. All cases in Europe were included to develop an epidemiological understanding of the disease and investigate several suspected risk factors, one being anorexigens.

Clinical Issues of the IPPH Study by m[illegible] of Review Panel: **Stuart Rich, M.D.,** Chief, Section of Cardiology, University of Illinois at Chicago, emphasized the extraordinary rarity of the disease, and its devastation; nearly 100% fatal in about 2 years. A number of risk factors have been identified, including obesity, use of anorexigens, systemic hypertension, and heredity.

Neuropharmacology, Neurotoxicity

Neurotoxicity and Efficacy of Fenfluramine: **Lewis Seiden, Ph.D.,** Professor of Pharmacology, Department of Pharmacological and Physiological Sciences, University of Chicago, Chicago, IL, proposed to review the neurotoxicity of fenfluramine in animals and potential neurotoxicity in humans. He shared his conclusion that the risks of fenfluramine were high, its potential as an appetite suppressant were low, and should be used with caution. He presented data supporting the conclusion that fenfluramine is toxic to 5-HT terminal causing long lasting reduction in markers and uptake sites in the brain.

Neurotoxicity with Fenfluramine: **Mark E. Molliver, M.D.,** Professor of Neuroscience & Neurology, Department of Neuroscience and Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, contended that his studies of the mechanisms of other amphetamine derivatives produce neurotoxic effects in the brain, and dexfenfluramine would have similar results. He showed data to demonstrate long term depletion of selectively vulnerable dorsal raphe axons.

FDA PRESENTATION

Medical Review: **Leo Lutwak, M.D., Ph.D.,** Division of Metabolism and Endocrine Drug Products, read each of the questions posed to the Committee, reviewed the sponsor's position on the data for each issue, and pointed out the different FDA analysis of each item.

Statistical Review: **Edward Nevius, Ph.D.,** presented an analysis of the data with the percent weight loss in the INDEX study, the largest, as a percentage weight loss from baseline. He reviewed the Guidance document criteria for analysis.

Neurotoxicology Review: **Joseph F. Contrera, Ph.D.,** Office of Research Resources, defined neurotoxicity as an adverse effect on the structure and function of the central and peripheral nervous system related to chemical exposure. He discussed the evidence of long lasting depletion of 5-HT and the brain concentration of dexfenfluramine in rats, and questioned whether there is a dose-related association.

Epidemiology and Aspects of a Phase IV Study: **Bruce V. Stadel, M.D., M.P.H.,** Division of Metabolism and Endocrine Drug Products, stated that stronger criteria are used for evaluating drug benefits than risks. He reminded that adverse event reports are examined to screen for possible trends. He discussed the risk of PPH and suggested that it is minimal. He suggested that the co-morbid and neurotoxicity questions are the leading issues for further study in a Phase IV setting.

Summary: **Gloria Troendle, M.D.,** Deputy Director, Division of Metabolism and Endocrine Drug Products, emphasized that this drug is for long term use. She displayed the numbers of patients in the trials who had lost 5, 10, and 15 percent of baseline weight and difference from placebo. She discussed the definition and number of responders in the studies, and listed the possible risks again.

Discussion and Questions: There was discussion of the FDA presentation and additional questions and discussion of the Sponsor and their consultants.

QUESTIONS

1. Is the evidence of efficacy sufficient to warrant approval of dexfenfluramine for long-term (indefinite) use, as proposed?
   Yes: 7 **No: 1**

2. Is the evidence of safety sufficient to warrant approval for long-term use, as proposed?
   Yes: 3 **No: 5**

3. If your answer to questions 1 and 2 is yes, do you recommend that a phase 4 study be done to provide further information on weight, mortality, and serious morbidity such as heart disease, diabetes and strokes? (Such a study might , for example, be a large, simple, randomized trial of at least 2-year duration).
   Yes: 8 **No: 0**

4. Are there any issues the committee recommends be addressed in labeling?
   Not addressed. Moot in light of split opinion on #1 and 2.

At this point, there was no clear directive for action from the Advisory Committee because of the split opinions on the safety and efficacy questions. In an effort to clarify the recommendation to the Agency, a new question was composed and asked of the members.

In evaluating the benefits and the risks of the drug and based on the data presented, would you recommend approval?

Yes: 3 **No: 2** **Not a recommendation.**

Three members of the Committee had left the meeting to get their air transportation home, so the posing of this question and the answer are not a bona fide recommendation because there was no longer a quorum of the Committee.

The meeting was adjourned at 5:38 pm.